

### Remarks

Claim 1 has been amended, no new matter has been introduced.

As previously stated, the claims are limited to 4-5 cyclization (i.e. cyclisation of compound II). The prior art discloses 5-6 cyclization using an azide reagent which causes enormous technical problems in large amounts. However, use of more convenient cyclization agents failed for 5-6 cyclization. Surprisingly, it has been found that when amino acids 4-5 are cyclized, safer and convenient cyclization agents can be used such as HOBT and HBTU and give in good yields and excellent purity. This is clearly unexpected and could not be predicted from the cited prior art.

The yields obtained for the cyclised peptide is 77% for the process step connecting amino acids 4 and 5; the product having 84% purity and no detectable epimerized by-product (see Example 3, HBTU method b)).

In contrast, under the same reaction conditions the process step connecting amino acids 5 and 6 yielded less than 20% cyclised peptide with only about 16% purity measured by HPLC. Such a crude product cannot be purified on a technical scale with reasonable effort.

The Applicants have amended claim 1 to further include cyclizing agents HOBT and HBTU.

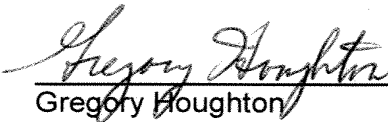
There is no hint in the prior art as to how to modify the manufacturing process for making compounds of formula I on larger scale by avoiding critical reagents and obtaining the product in good yields and with high purity.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. 103 be withdrawn.

Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

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